CLAIMS

We claim:

1. A method of prolonging expression of a heterologous gene in a cell infected with a vector encoding the heterologous gene comprising

a) infecting the cell with a vector encoding an apoptosis inhibiting agent.

2. The method of claim 1, wherein the heterologous gene encodes a prodrug activating enzyme.

3. The method of claim 2 further comprising contacting the infected cell of step a) with a prodrug.

4. The method of claim 2 or claim 3, wherein the cell is a neoplastic cell or a tumor-associated endothelial cell.

5. The method of claim 4, wherein the apoptosis inhibiting agent is a caspase pathway inhibiting agent.

6. The method of claim 5, wherein the caspase pathway inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, Survivin, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFIAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP and ScIAP.

7. The method of claim 3, wherein the prodrug activating enzyme is selected from the group consisting of cytochrome P450, NADPH-P450 reductase, thymidine kinase, cytosine deaminase, nitroreductase, thymidine phosphorylase, purine nucleoside phosphorylase, alkaline phosphatase, carboxypeptidase A, carboxypeptidase G2, linamarase, beta-lactamase, xanthine oxidase, guanine phosphoribosyl transferase (GPT), deoxycytidine kinase, uracil phosphoribosyltransferase, carboxylesterase, and folylpolyglutamate synthetase.

8. The method of claim 3, wherein the prodrug is selected from the group consisting of cyclophosphamide (CPA) and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase; ganciclovir, acyclovir and their

analogs; 5-fluorocytosine; CB1954 and other aromatic nitro prodrugs; 5'-deoxy-5-fluorouridine; 6-methylpurine-2'-deoxynucleoside; etoposide phosphate; methotrexate-(phenyl)alanine; benzoic acid mustard-glucuronide; amygdalin; cephalosporin-mustard carbamate; xanthine; 6-thioxanthine; cytosine arabinoside; 5-fluorouracil; irinotecan (CPT-11); edatrexate.

9. The method of claim 3, wherein the prodrug activating enzyme is cytochrome P450 and the prodrug is cyclophosphamide or ifosfamide.

10. The method of claim 9, wherein the cytochrome P450 enzyme is selected from the group consisting of CYP 1A1, 1A2, 2A6, 2B1, 2B2, 2B4, 2B5, 2B6, 2B11, 2C3, 2C5, 2C6, 2C7, 2C8, 2C9, 2C11, 2C18, 2C19, 2D6, 2E1, 3A1, 3A2, 3A4, 3A5, 3A7 and 4A11.

11. A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target cell in a mammal in need thereof comprising the steps of:

a) infecting the target cell with a first vector comprising a nucleic acid encoding a prodrug activating enzyme;

b) infecting the target cell with a second vector comprising a nucleic acid encoding an apoptosis inhibiting agent; and

c) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a).

12. The method of claim 11, wherein the target cell is a neoplastic cell or a tumor-associated endothelial cell.

13. A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target cell in a mammal in need thereof comprising the steps of:

a) infecting the target cell with a vector comprising a nucleic acid encoding a prodrug activating enzyme and a nucleic acid encoding an apoptosis inhibiting agent; and

b) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a).

14. The method of claim 11 or claim 13, wherein the apoptosis inhibiting agent is expressed under control of a regulatable promoter.

15. The method of claim 11, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a factor that promotes apoptosis expressed under control of a regulatable promoter.

16. The method of claim 15, wherein the factor that promotes apoptosis is selected from the group consisting of Smac/Diablo, a caspase, p53, Bax, Bak, Bcl-Xs, Bad, Bik, Bid, apoptosis inducing factor, anti-sense or siRNA directed against the apoptosis inhibiting agent, or against an IAP or other anti-apoptotic factor.

17. The method of claim 13, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a death receptor ligand expressed under control of a regulatable promoter.

18. The method of claim 17, wherein the death receptor ligand is selected from the group consisting of TNFα, Trail and Fas ligand.

19. The method of claim 1, wherein the heterologous gene encodes a soluble, or secretable, therapeutic factor.

20. The method of claim 19, wherein the therapeutic factor has anti-angiogenic, cytotoxic or immune modulatory activity.

21. The method of claim 19 or claim 20, wherein the cell is a neoplastic cell or a tumor-associated endothelial cell.

22. The method of claim 21, wherein the factor is selected from the group consisting of endostatin, angiostatin, VEGF antibody, VEGF receptor-derived ectodomain, tumstatin and other integrin-binding or integrin-inhibiting molecules, 16 kd prolactin fragment, platelet factor 4 and antibody, anti-sense agents or siRNA directed against

angiogenic factors, the tumor necrosis factor superfamily, including TNFα, Fas ligand and Trail, a cytokine, interferon α, interferon β and interleukins 2, 12 and 18.

23. A method of increasing the concentration of a soluble, or secretable, therapeutic factor in a target cell, in a mammal in need thereof comprising the steps of:

a) infecting the target cell with a vector comprising a nucleic acid encoding a soluble, or secretable, factor and a nucleic acid encoding an apoptosis inhibiting agent.

24. A method of increasing the concentration of a soluble, or secretable, therapeutic factor in the vicinity of a target cell in a mammal in need thereof comprising the steps of:

a) infecting the target cell with a first vector comprising a nucleic acid encoding a soluble, or secretable, therapeutic factor; and

b) further infecting the target cell with a nucleic acid encoding an apoptosis inhibiting agent, wherein said nucleic acid encoding and apoptosis inhibiting agent can be present in the first vector or in a separate vector.

25. The method of claim 23 or claim 24, wherein the soluble, or secretable therapeutic factor has anti-angiogenic, cytotoxic or immune modulatory activity.

26. The method of claim 25, wherein the target cell is a neoplastic cell or a tumor-associated endothelial cell.

27. The method of claim 26, wherein the soluble or secretable therapeutic factor is selected from the group consisting of endostatin, angiostatin, VEGF antibody, VEGF receptor-derived ectodomain, tumstatin, 16 kd prolactin fragment, platelet factor 4.

28. The method of claim 26, wherein the soluble or secretable therapeutic factor is an integra-binding molecule, an integrin inhibiting molecule, an antibody, anti-sense or siRNA directed against angiogenic factors, the tumor necrosis factor superfamily, including TNFα, Fas ligand and Trail, a cytokine, interferon α, interferon β, interleukin 2, interleukin 12 and interleukin 18.

29. The method of claim 23 or claim 24, wherein the apoptosis inhibiting agent is selected from the group consisting of caspase inhibitors, anti-apoptotic Bcl-2 family members and death receptor pathway inhibitory molecules.

30. The method of claim 29, wherein the death receptor pathway inhibitory molecule is selected from the group consisting of Fas-associated death domain-like ice inhibitory proteins (vFLIPs and cFLIPs), death receptor decoy receptors (DcR's), and dominant-negative Fas-associated death domain proteins (FADDs).

31. The method of claim 5, wherein the caspase pathway inhibiting agent is selected from the group consisting of anti-apoptotic Bcl-2 family members, FAS-associated death domain-like ice inhibitory proteins (vFLIPS and cFLIPs), death receptor decoy receptors (DcR's) and dominant-negative Fas-associated death domain proteins (FADDs).

32. A method of increasing vector spread in a host containing a vector encoding a heterologous gene comprising administering a replicating vector and administering a non-replicating vector encoding an apoptosis inhibiting agent and a heterologous gene, with the non-replicating vector administered prior to, concurrent with, or after the replicating vector.

33. The method of claim 32, wherein the replicating vector is an adenovirus.

34. The method of claim 32, wherein the apoptosis inhibiting agent is selected from the group consisting of caspase inhibitors, anti-apoptotic Bcl-2 family members and death receptor pathway inhibitory molecules.

35. The method of 32, wherein the apoptosis inhibiting agent is p35.